REMARKS

Applicant submits this Amendment in response to the Office Action mailed on February 9, 2007.

The claims have been amended as follows. Independent claim 1 has been amended to call for a selective estrogen beta receptor agonist that has a potency higher than that of genistein. Support for "selective" estrogen beta receptor agonist is found throughout the specification, such as on page 5, lines 19-20. Support for potency higher than genistein is found throughout the specification as the specification discloses all estrogen beta receptor agonists, including genistein and estrogen beta receptor agonists that are more potent than genistein. Potency of several estrogen beta receptor agonists compared to genistein, and having a potency greater than that of genistein, is shown in the graph of Figure 6. Claim 8 has been amended to remove the term "genistein" in view of the amendment to claim 1.

Rejections of the Claims

A. 35 U.S.C. §102(b)

I. Anthony, Am. Soc. For Nutritional Sciences J. Nutr., 130:662S-663S (2000)

The Examiner has rejected claims 1, 2, and 8 as being anticipated by the disclosure of Anthony, Am. Soc. For Nutritional Sciences J. Nutr., 130:662S-663S (2000). Applicant traverses the rejection of these claims on this ground.

Anthony discloses that soy, which contains genistein, may contribute to a reduction in coronary vasospasm and thrombosis. Applicant submits that Anthony is not pertinent to the present invention.

The present claims call for a method for reducing the incidence or severity of vascular hyperreactivity. As defined in the specification, vascular hyperreactivity refers to an exaggerated amplitude and/or duration of a constrictor response to a vasoactive substance. As stated on page 9 of the present application, "The term "vasospasm" is often misused in the literature to refer to a vasoconstriction which, rather than being abnormal and life-threatening, is a normal, healthy contraction as a means of autoregulating blood flow." This alternate definition of vasospasm is what is used in Anthony. That this is so is clear from the context of Anthony and from the literature cited by Anthony when referring to vasospasms. Anthony cites Williams and Clarkson, Schoene and Guidry, and Helmeste and Tang, each of which utilizes the definition of vasospasm which is different from that of the present application.

That vasospasm as used incorrectly in the prior art refers to a physiological event, rather than a pathological event as defined in the present application, is clear from the Anthony article itself. On page 663S, first column, last four lines of the first full paragraph, Anthony states that isoflavones might have the beneficial effects of inhibiting platelet activation and aggregation and of reducing the amount of serotonin. In the absence of isoflavones, these factors contribute to a reduction in (physiological) coronary vasospasm and contribute to thrombosis.

Thus, Anthony states that the isoflavones are beneficial because of their effect on inhibiting platelets and reducing serotonin levels, and thereby preventing the deleterious reduction in coronary vasospasms and thrombosis that are caused by the platelets and serotonin. Because Anthony discloses the use of soy (genistein) for the removal of factors that prevent the occurrence of a physiologic event, and whereas the present invention pertains to the control of a pathologic event, Applicant submits that Anthony is not pertinent to the prior art.

In addition, the claims as amended herein, call for an estrogen beta receptor agonist that has a potency that is higher than that of genistein. As shown in the present application in Figure 6, certain estrogen beta receptor agonists, including 3βAdiol, have a potency higher than that of genistein. The disclosure of Anthony is restricted to genistein.

Because Anthony does not disclose the features called for in the present claims, Applicant submits that the rejection of claims 1, 2, and 8 as being anticipated by the disclosure of Anthony is overcome and the Examiner is requested to withdraw the rejection of these claims on this ground.

II. Kim, J. Neurosurgery, 89:289-296 (1998)

The Examiner has rejected claims 1-3 and 8 as being anticipated by the disclosure of Kim, J. Neurosurgery, 89:289-296 (1998). Applicant traverses the rejection of these claims on this ground.

Preliminarily, Applicant respectfully submits that the Examiner has misread the disclosure of Kim. The Examiner states in the Office Action that Kim teaches that coronary vasospasm, a persistent narrowing of major cerebral arteries, is followed by subarachnoid hemorrhage. It is respectfully pointed out that Kim does not disclose coronary vasospasm, but rather discloses cerebral vasospasm.

Claims 2 and 3 call for vascular beds other than cerebral and it is submitted, therefore, that the rejection of these claims as being anticipated by the disclosure of Kim is improper. Moreover, independent claim 1 has been amended to call for an estrogen beta receptor

agonist having a potency higher than that of genistein. Kim does not disclose an estrogen beta receptor agonist other than genistein.

Accordingly, it is submitted that the rejection of claims 1-3 and 8 as being anticipated by the disclosure of Kim is overcome and the Examiner is requested to withdraw the rejection of these claims on this ground.

III. Honore, Fertility and Sterility, 67(1):148-154 (1997)

The Examiner has rejected claims 1-3, 8, 15, and 16 as being anticipated by the disclosure of Honore, Fertility and Sterility, 67(1):148-154 (1997). Applicant traverses the rejection of these claims on this ground.

Like Anthony, Honore is concerned, not with vasospasms and hyperreactivity as these terms are defined in the present application, but with vasospasms as this term is often used in the prior art, that is to mean a desirable physiological process that is reduced with certain diseases such as atherosclerosis. See Honore, page 149, first column, second full paragraph, and see the present specification on page 9, line 11. Honore is concerned with the decrease in physiologic coronary artery vascular reactivity that occurs with such pathologic conditions such as atherosclerosis. The present invention, in contrast, is concerned with vasospasms and other manifestations of vascular hyperreactivity, which is an undesirable pathologic process that is distinct from the physiologic vasospasms, as this term is used in the prior art. Thus, it is submitted that the Honore reference is not pertinent to the present invention.

Moreover, as discussed above in relation to the other cited references, Honore discloses genistein. The claims of the present application call for an estrogen beta receptor

agonist that has a potency higher than that of genistein. Therefore, the present claims call for a class of estrogen beta receptor agonists that does not include genistein.

For these reasons, Applicant submits that the prior art does not disclose or suggest all of the features of the present claims. The Examiner is, accordingly, respectfully requested to reconsider and to withdraw the rejection of claims 1-3, 8, 15, and 16 as being anticipated by the disclosure of Honore.

B. 35 U.S.C. 103(a)

I. Anthony, Am. Soc. For Nutritional Sciences J. Nutr., 130:662S-663S (2000) and Weihua, PNAS, 99:13589-13594 (2002)

The Examiner has rejected claims 1, and 4-6 under 35 U.S.C. §103(a) as being obvious in view of the combined disclosures of Anthony, Am. Soc. For Nutritional Sciences J. Nutr., 130:662S-663S (2000) and Weihua, PNAS, 99:13589-13594 (2002). Applicant traverses the rejection of these claims on this ground.

As discussed above, Anthony is not pertinent to the present invention because Anthony discloses physiologic vasoconstrictions rather than pathologic vascular hyperreactivity as called for in the present claims and because the disclosure of Anthony is limited to genistein. The secondary reference, Weihua, discloses that 5α-androstane-3β,17β-diol is an estrogen beta receptor ligand.

It is respectfully submitted that the present invention is not disclosed or suggested by the combined disclosures of Anthony and Weihua. Neither Anthony nor Weihua disclose or

suggest that an estrogen beta receptor agonist has an effect to reduce the incidence or severity of pathological vascular hyperreactivity, as presently claimed.

Moreover, it is submitted that the Examiner's statement that it would be obvious to one of ordinary skill in the art to administer 5α-androstane-3β,17β-diol in place of genistein is erroneous. Genistein is a relatively unique estrogen beta receptor agonist because it is a protein tyrosine kinase inhibitor (see Kim, J. Neurosurgery, 89:289-296 (1998), cited by Examiner). 5α-androstane-3β,17β-diol is not a protein tyrosine kinase inhibitor. Because 5α-androstane-3β,17β-diol and genistein have different activities, one skilled in the art would not necessarily understand that 5α-androstane-3β,17β-diol could be substituted in place of genistein. It is only by the teaching of the present application that would alert one of skill in the art that genistein or 5α-androstane-3β,17β-diol may be used to combat vascular hyperreactivity.

Applicant submits that the combined teachings of Anthony and Weihua does not disclose or suggest the present invention and that the combination of these two references is improper. Accordingly, Applicant submits that the rejection of claims 1 and 4-6 as being obvious in view of the combined disclosures of Anthony and Weihua is improper and Applicant respectfully requests the Examiner to reconsider and to withdraw the rejection of these claims on this ground.

II. Anthony, Am. Soc. For Nutritional Sciences J. Nutr., 130:662S-663S (2000); Weihua, PNAS, 99:13589-13594 (2002); and Fujikawa, J. of Cerebral Flow and Metabolism, 19:44-52 (1999)

The Examiner has rejected claims 1, and 9, 10, 13, and 14 under 35 U.S.C. §103(a) as being obvious in view of the combined disclosures of Anthony, Am. Soc. For Nutritional Sciences J. Nutr., 130:662S-663S (2000); Weihua, PNAS, 99:13589-13594 (2002); and Fujikawa, J. of Cerebral Flow and Metabolism, 19:44-52 (1999). Applicant traverses the rejection of these claims on this ground.

The disclosures of Anthony and Weihua are discussed above. Anthony pertains to genistein. Weihua pertains to 5α-androstane-3β,17β-diol. Fujikawa discloses that cerebral vasospasms are induced by the tyrosine kinase pathway, which is inhibited by genistein. As stated above and as disclosed in Fujikawa, genistein is a protein kinase inhibitor. See Fujikawa, page 45, lines 1-7. Further, as taught in Fujikawa in the Discussion section: "Thus, the dilation of the spastic basilar artery by genistein does not result from the inhibition of MLCK but is closely associated with the decrease in phosphorylation of intracellular substrates of tyrosine kinase, Shc."

It is clear from the disclosure of Fujikawa that genistein has actions other than those related to estrogen beta receptor agonism. Genistein, unlike 5α-androstane-3β,17β-diol, is a tyrosine kinase inhibitor. It is this property of genistein that is disclosed in Fujikawa to be that which is responsible for genistein's activity pertaining to the dilation of the spastic basilar artery.

It is respectfully submitted that one skilled in the art would not extend the disclosure of Fujikawa of the protein kinase inhibitory property of genistein to expect that

estrogen beta receptor agonists which do not share this property could be used to reduce vascular hyperreactivity, as is presently claimed. There is no teaching in the prior art that estrogen beta receptor agonists that do not have protein kinase inhibitory properties, such as 5α-androstane-3β,17β-diol, may be useful to reduce vascular hyperreactivity.

In view of the above, Applicant submits that claims 1, and 9, 10, 13, and 14 are not obvious in view of the combined disclosures of Anthony, Weihua, and Fujikawa. The Examiner is respectfully requested to reconsider and to withdraw the rejection of these claims on this ground.

III. Anthony, Am. Soc. For Nutritional Sciences J. Nutr., 130:662S-663S (2000) and Barkheim, Molecular Physiology, 54:105-112 (1998)

The Examiner has rejected claims 1 and 7 under 35 U.S.C. §103(a) as being obvious in view of the combined disclosures of Anthony, Am. Soc. For Nutritional Sciences J. Nutr., 130:662S-663S (2000) and Barkheim, Molecular Physiology, 54:105-112 (1998). Applicant traverses the rejection of these claims on this ground.

The disclosure of Anthony is discussed above. Anthony pertains solely to genistein, a compound that has protein kinase inhibitory properties, in addition to its activity as an estrogen beta receptor agonist. Anthony also pertains to preventing the inhibition of vasoconstrictions that are physiologic, rather than preventing the occurrence of pathologic vascular hyperreactivity, as is presently claimed. Barkheim discloses that epiestriol is an estrogen beta receptor agonist.

It is submitted that neither Anthony nor Barkheim, nor the combination of Anthony and Barkheim, discloses or suggests that an estrogen beta receptor agonist may be useful in reducing the incidence or severity of pathologic vascular hyperreactivity, as called for in the present claims. Moreover, since it is well known that genistein has properties other than estrogen beta receptor agonism, such as protein kinase inhibition, one skilled in the art would not expect that the teachings concerning genistein could be extrapolated to other estrogen beta receptor agonists not sharing the other properties of genistein.

Accordingly, the Examiner is respectfully requested to reconsider the rejection of claims 1 and 7 as being obvious in view of the combined disclosures of Anthony and Barkheim and to withdraw the rejection of these claims on this ground.

IV. Honore, Fertility and Sterility, 67(1):148-154 (1997)

The Examiner has rejected claims 1, 11, and 12 under 35 U.S.C. §103(a) as being obvious in view of the disclosure of Honore, Fertility and Sterility, 67(1):148-154 (1997). Applicant traverses the rejection of these claims on this ground.

As acknowledged by the Examiner, Honore teaches that atherosclerosis may impair coronary artery dilation and that genistein may improve coronary vascular reactivity. This teaching of Honore underscores the distinction between the invention and the teachings of the various prior art references cited by the Examiner.

The present invention pertains to pathologic hyperreactivity. As recited in the present claims, the beta receptor agonist of the invention reduces vascular hyperreactivity. The genistein of Honore increases coronary vascular reactivity.

As stated in the specification on pages 9 and 10, the vascular reactivity referred to in the prior art and the vascular hyperreactivity of the present invention are two markedly different phenomena. The vascular reactivity of the prior art, which is vasodilation, is a physiologic process that it is of benefit to enhance. The prior art discloses that genistein enhances this physiologic vascular reactivity.

In contrast, the method of the invention pertains to the reduction of pathologic vascular hyperreactivity, i.e. excess vasoconstriction. In contrast to the beneficial enhancement of vascular reactivity, i.e. vasodilation, that is the object of the prior art, it is desirable to reduce or eliminate the vascular hyperreactivity, i.e. excess vasoconstriction, that is the object of the method of the present invention. It is submitted, therefore, that Honore is not pertinent to the present invention.

The Examiner is requested to reconsider and to withdraw the rejection of claims 1, 11, and 12 as being obvious in view of the disclosure of Honore.

CONCLUSION

Applicant submits that the claims, as amended herein, are in condition for allowance and request an early notice to that effect.

Respectfully submitted,

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, PO Box 1450, Alexandria, VA 22313-1450, on May 7, 2007.

Dated: 5/7/07

Howard M. Eisenberg